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Tumor Necrosis Factor Family

TUMOR NECROSIS FACTOR FAMILY

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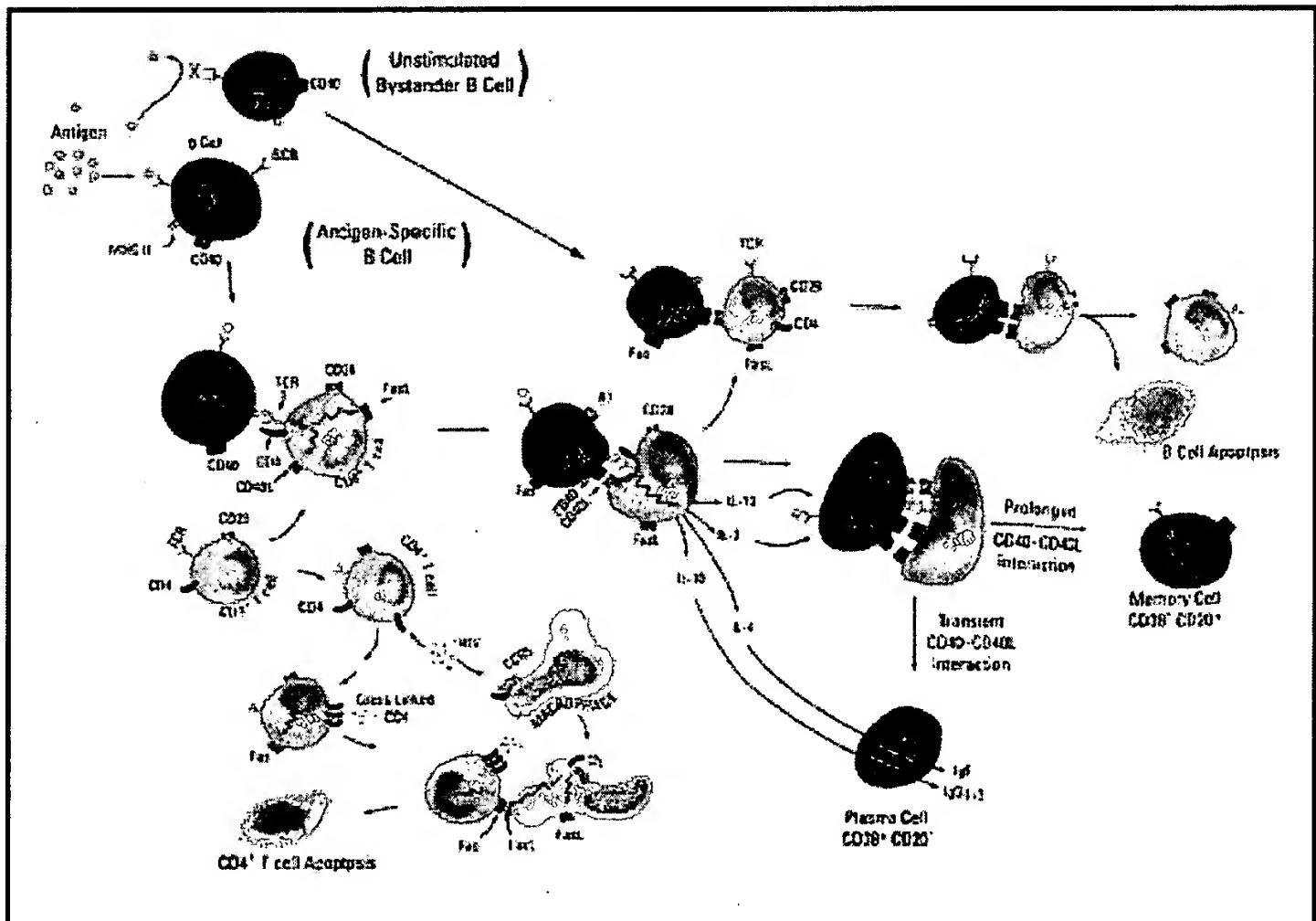


Fig. 1. TNF Superfamily involving Fas/FasL and CD40/CD40L.

Overview

The first suggestion that a tumor necrotizing molecule existed was made when it was observed that cancer patients occasionally showed spontaneous regression of their tumors following bacterial infections.¹ Subsequent studies in the 1960s indicated that host-associated (or endogenous) mediators, manufactured in response to bacterial products, were likely responsible for the observed effects.^{2, 3} In 1975 it was shown that a bacterially-induced circulating factor had strong anti-tumor activity against tumors implanted in the skin in mice.^{2, 4} This factor, designated tumor necrosis factor (TNF), was subsequently isolated,⁵ cloned,⁶ and found to be the prototype of a family of molecules that are involved with immune regulation and inflammation.^{2, 7, 8} The receptors for TNF and the other members of the TNF superfamily also constitute a superfamily of related proteins.⁹⁻¹² Since a number of reviews have been published on the TNF superfamily (TNFSF) and the TNF receptor superfamily (TNFRSF),^{2, 7-13} this review is designed only to provide simple, basic background information on all of the currently known receptors and ligands in this superfamily.

Ligands/Co-Receptors

TNF-related ligands usually share a number of common features. These features do not include a high degree of overall amino acid (aa) sequence homology.^{7, 9} With the exception of nerve growth factor (NGF) and TNF-beta, all ligands are synthesized as type II transmembrane proteins (extracellular C-terminus) that contain a short cytoplasmic segment (10-80 aa residues) and a relatively long extracellular region (140-215 aa residues).⁷ NGF, which is structurally unrelated to TNF, is included in this superfamily only because of its ability to bind to the TNFRSF low affinity NGF receptor (LNGFR). NGF has a classic signal sequence peptide and is secreted. TNF-beta, in contrast, although also fully secreted, has a primary structure much more related to type II transmembrane proteins. TNF-beta might be considered as a type II protein with a non-functional, or inefficient, transmembrane segment.^{7, 8} In general, TNFSF members form trimeric structures, and their monomers are composed of beta-strands that orient themselves into a two sheet structure.^{8, 10, 11} As a consequence of the trimeric structure of these molecules, it is suggested that the ligands and receptors of the TNFS and TNFRSF superfamilies undergo "clustering" during signal transduction.^{11, 13}

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NGF:

Human NGF is a 12.5 kDa, nonglycosylated polypeptide 120 aa residues long.^{14, 15} Synthesized as a prepropeptide, there is an 18 aa residue signal sequence, a 103 aa residue N-terminal pro-sequence, and a 120 aa residue mature segment. Human to mouse, there is 90% aa sequence identity in the mature segment. In the mouse, NGF is referred to as beta-NGF, due to the existence of NGF in a 130 kDa (7S) heterotrimeric ($\alpha\beta\gamma$) complex in submaxillary glands.^{15, 16} Many cells, however, do not synthesize all the components of this 7S complex, and the typical form for NGF is a 25 kDa, non-disulfide linked homodimer.^{14, 16} NGF and all other neurotrophins bind to the LNGFR, a member of the TNFRSF.¹⁷

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CD40L:

Human CD40L is a 39 kDa, type II (extracellular C-terminus) transmembrane glycoprotein that was originally identified on the surface of CD4⁺ T cells.¹⁸ With a predicted molecular weight of 29 kDa, CD40L is 261 aa residues long, with a 22 aa residue cytoplasmic domain, a 24 aa residue transmembrane segment, and a 215 aa residue extracellular region.¹⁸ Human to mouse, CD40L is 73% identical at the aa sequence level and mouse CD40L is apparently active in humans.¹⁹ Although usually considered to be a membrane bound protein, natural, proteolytically cleaved 15-18 kDa soluble forms of CD40L with full biological activity have also been described.^{20, 21} Like TNF-alpha, CD40L is reported to form natural trimeric structures.^{20, 22} Cells known to express CD40L include B cells, CD4⁺ and CD8⁺ T cells,²³ mast cells and basophils,²⁴ eosinophils,²⁵ dendritic cells,²⁶ and monocytes, NK cells, and gd T cells.²⁷

CD137L/4-1BBL:

Mouse 4-1BBL is a 50 kDa, 309 aa residue transmembrane glycoprotein that is the largest of the TNFSF members.²⁸ With a predicted molecular weight of 34 kDa, the molecule has an 82 aa residue cytoplasmic

region, a 21 aa residue transmembrane segment, and a 206 aa residue extracellular domain. Although human and mouse 4-1BB molecules exhibit 60% identity at the aa level, human and mouse 4-1BBL molecules exhibit only 36% identity at the aa level. This level of cross species conservation is much lower than that shown by other members of the TNFSF.^{11, 29} In mice, two ligands are known for 4-1BB: 4-1BBL and laminin.³⁰ Cells known to express 4-1BBL include B cells, dendritic cells, and macrophages.^{31, 32}

TNF-alpha

:

Human TNF-alpha is a 233 aa residue, nonglycosylated polypeptide that exists as either a transmembrane or soluble protein.^{6, 33, 34} When expressed as a 26 kDa membrane bound protein, TNF-alpha consists of a 29 aa residue cytoplasmic domain, a 28 aa residue transmembrane segment, and a 176 aa residue extracellular region.^{7, 33} The soluble protein is created by a proteolytic cleavage event via an 85 kDa TNF-alpha converting enzyme (TACE),^{35, 36} which generates a 17 kDa, 157 aa residue molecule that normally circulates as a homotrimer.^{6, 37, 38} Normal levels of circulating TNF are reported to be in the 10-80 pg/mL range.^{39, 40} While both membrane-bound and soluble TNF-alpha are biologically active, soluble TNF-alpha is reported to be more potent.⁴¹ Mouse to human, full-length TNF-alpha shows 79% aa sequence identity.^{42, 43} Unlike human TNF-alpha, mouse TNF-alpha is glycosylated.^{42, 43} The variety of cell types known to express TNF-alpha is enormous and includes macrophages, CD4⁺ and CD8⁺ T cells,⁴⁴ adipocytes,⁴⁵ keratinocytes,⁴⁶ mammary and colon epithelium,^{47, 48} osteoblasts,⁴⁹ mast cells,⁵⁰ dendritic cells,⁵¹ pancreatic beta-cells,⁵² astrocytes,⁵³ neurons,⁵⁴ monocytes,⁵⁵ and steroid-producing cells of the adrenal zona reticularis.⁵⁶

CD134L/OX40L:

OX40, the receptor for OX40L, is a T cell activation marker with limited expression that seems to promote the survival (and perhaps prolong the immune response) of CD4⁺ T cells at sites of inflammation.⁵⁷ OX40L also shows limited expression. Currently only activated CD4⁺, CD8⁺ T cells,⁵⁸ B cells,^{59, 60} and vascular endothelial cells have been reported to express this factor.⁶¹ The human ligand is a 32 kDa, 183 aa residue glycosylated polypeptide that consists of a 21 aa residue cytoplasmic domain, a 23 aa residue transmembrane segment, and a 139 aa residue extracellular region.^{7, 57} When compared to the extracellular region of TNF-alpha, OX40L has only 15% aa sequence identity, again emphasizing the importance of secondary and tertiary structures as the basis for inclusion in the TNF Superfamily.⁵⁷ Human OX40L is 46% identical to mouse OX40L at the aa sequence level. Mouse OX40L is active in humans, but human OX40L is inactive in mice.⁵⁸ Consistent with other TNFSF members, OX40L is reported to exist as a trimer.⁶²

CD27L/CD70:

Human CD27L is a 50 kDa, 193 aa residue type II (extracellular C-terminus) transmembrane glycoprotein that appears to have a very limited immune system expression pattern.^{63, 64} Having less than 25% aa sequence identity to TNF-alpha and CD40L, the molecule has only a 20 aa residue cytoplasmic segment, an 18 aa residue transmembrane domain, and a 155 aa residue extracellular region.⁶⁴ Although the 20 aa residue cytoplasmic segment is short by most standards, there is a suggestion that it has a signaling function, perhaps activating the cytolytic program of gd T cells⁶⁵ and/or contributing necessary signals for antibody production in B cells.⁶⁶ Cells known to express CD27L are usually activated cells and include NK cells,⁶⁷ B cells,⁶⁶ CD45RO⁺, CD4⁺ and CD8⁺ T cells,⁶⁸ gd T cells,⁶⁵ and certain types of leukemic B cells.⁶⁹

FasL:

Fas ligand (FasL) is a highly conserved, 40 kDa transmembrane glycoprotein that occurs as either a membrane bound protein or a circulating homotrimer.^{70, 71} In humans, FasL is synthesized as a 281 aa residue protein with an 80 aa residue cytoplasmic region, a 22 aa residue transmembrane segment, and a 179 aa residue extracellular domain.⁷⁰ When proteolytically cleaved, FasL is a 70 kDa homotrimer composed of 26 kDa monomers with full biological activity.⁷¹ In mice, the FasL is somewhat different. Although mouse FasL molecule has 77% aa sequence identity with human FasL,^{70, 72, 73} polymorphisms exist in the mouse FasL, leading to functionally distinct FasL forms.⁷⁴ In addition, a one aa residue substitution at position 273 (Phe to Leu) results in the *gld/gld* (generalized lymphoproliferative disease) mutation.⁷² Finally, while FasL in a membrane-bound form shows species cross-reactivity,⁷⁰ soluble mouse FasL is apparently biologically inactive.⁷¹ Cells known to express FasL include type II pneumocytes

and bronchial epithelium,⁷⁵ monocytes,⁷⁶ LAK cells and NK cells,^{77, 78} dendritic cells,⁷⁹ B cells,⁸⁰ macrophages,⁸¹ CD4⁺ and CD8⁺ T cells,⁸² and colon and lung carcinoma cells.^{75, 83}

CD30L:

Human CD30L is a 40 kDa, 234 aa residue transmembrane glycoprotein with 72% aa sequence identity to its mouse counterpart.⁸⁴ With a predicted molecular weight of 26 kDa, the molecule consists of a 46 aa residue cytoplasmic region, a 21 aa residue transmembrane segment, and a 172 aa residue extracellular domain.⁸⁴ Species cross-reactivity has been reported.⁸⁴ As suggested for CD27L, the cytoplasmic region is suggested to transduce a signal.⁸⁵ The CD30/CD30L system is complex since CD30 ligation can induce both proliferation and apoptosis.⁸⁴ Cells known to express CD30L include monocytes and macrophages,⁸⁴ B cells plus activated CD4⁺ and CD8⁺ T cells,⁸⁶ neutrophils, megakaryocytes, resting CD2⁺ T cells, erythroid precursors,⁸⁷ and eosinophils.⁸⁸

TNF-beta/LT-alpha

:

TNF-beta, otherwise known as lymphotoxin-alpha (LT-alpha) is a molecule whose cloning was contemporary with that of TNF-alpha.⁸⁹ Although TNF-beta circulates as a 171 aa residue, 25 kDa glycosylated polypeptide, a larger form has been found that is 194 aa residues long.⁹⁰ The human TNF-beta cDNA codes for an open reading frame of 205 aa residues (202 in the mouse),^{89, 91} and presumably some type of proteolytic processing occurs during secretion. As with TNF-alpha, circulating TNF-beta exists as a non-covalently linked trimer and is known to bind to the same receptors as TNF-alpha.⁹²⁻⁹⁵ Circulating TNF-beta levels are reported to be about 150 pg/mL.⁹⁶ Human TNF-beta is 72% identical to mouse TNF-beta at the aa sequence level across the entire molecule.⁹¹ TNF-alpha to TNF-beta, aa sequence identity is reported to be 28%.^{6, 93} Unlike TNF-alpha, TNF-beta does not have a transmembrane form. However, it can be membrane-associated, due to its binding to membrane-anchored LT-beta (see below).^{92, 97} In this complex, TNF-beta and LT-beta will form a heterotrimer that binds to both the LT-beta receptor and TNFRI receptor. Activation of the TNFRI receptor, however, does not occur.^{92, 94} Cells known to express TNF-beta include NK cells, T cells and B cells.⁹⁷

LT-beta:

Human lymphotoxin-beta (LT-beta), also known as p33, is a 33 kDa type II (extracellular C-terminus) transmembrane glycoprotein originally cloned from a T cell hybridoma cell line. It is 244 aa residues long, and has a 16 aa residue cytoplasmic segment, a 31 aa residue transmembrane domain, and a 197 aa residue extracellular region.^{7, 98} On the membrane surface, LT-beta readily forms a trimeric complex with TNF-beta, in either a 2:1 (major form) or a 1:2 (minor form) ratio.^{92, 98} LT-beta is not secreted.⁹⁴ A comparison of human to mouse LT-beta shows 80% aa sequence identity in homologous regions.⁹⁹ Overall, however, the mouse gene shows significant differences from the human gene. In mice, an intron has been incorporated into the genome creating a 66 aa residue insert into what would otherwise be a 240 aa residue molecule.¹⁰⁰

TRAIL:

TRAIL, or TNF-related apoptosis-inducing ligand, is a newly discovered TNFSF member initially cloned from human heart and lymphocyte cDNA libraries.¹⁰¹ With a predicted molecular weight of 32 kDa, human TRAIL is 281 aa residues long, with a 17 aa residue cytoplasmic tail, a 21 aa residue transmembrane segment, and 243 aa residue extracellular region.^{101, 102} Human TRAIL is 65% identical to mouse TRAIL at the aa sequence level across the entire molecule and there is complete species cross-reactivity.¹⁰¹ As a membrane bound protein, TRAIL shows a trimeric structure.¹⁰² Although TRAIL is known to be expressed by lymphocytes, many tissues seem to express the ligand, and this broad expression pattern suggests an intriguing function for the molecule.¹⁰¹

Receptors

As with members of the TNF Superfamily, members of the TNF Receptor Superfamily (TNFRSF) also share a number of common features. In particular, molecules in the TNFRSF are all type I (N-terminus extracellular) transmembrane glycoproteins that contain one to six ligand-binding, 40 aa residue cysteine-rich motifs in their extracellular domain.^{7, 9-11} In addition, functional TNFRSF members are usually trimeric or multimeric complexes that are stabilized by intracysteine disulfide bonds. Unlike most

members of the TNFSF, TNFRSF members exist in both membrane-bound and soluble forms.⁹ Finally, although aa sequence homology in the cytoplasmic domains of the superfamily members does not exceed 25%,⁷ a number of receptors are able to transduce apoptotic signals in a variety of cells, suggesting a common function.^{9, 103}

LNGFR/p75:

The human low-affinity nerve growth factor receptor (LNGFR) is a 75 kDa, 427 aa residue type I (extracellular N-terminus) transmembrane glycoprotein. The 427 aa residue receptor contains a 25 aa residue signal sequence, a 225 extracellular region, a 23 aa residue transmembrane segment, and a 154 aa residue cytoplasmic domain.^{7, 104, 105} There are four cysteine-rich domains in its extracellular region. A comparison of human to rat LNGFR shows 92% aa sequence identity in the extracellular domain, and 95% aa sequence identity in the cytoplasmic region.^{104, 106} In its functional form, it often appears as an approximately 200 kDa disulfide-linked homodimer.^{104, 105} All neurotrophins bind to LNGFR with the same K_d of approximately 1-3 nM.^{17, 105, 106} In contrast to the high-affinity neurotrophin receptors (Trks), LNGFR has no inherent tyrosine kinase activity.¹⁰⁷ It has been suggested that LNGFR passes NGF to the physiologically-active Trks.^{108, 109} However, recent evidence now suggests that co-expressed LNGFR and TrkA modulate each others activities^{110, 111} and that LNGFR signals on its own, utilizing a functional "death domain" in its cytoplasmic region.^{112, 113} Soluble forms of 35- 45 kDa LNGFR are known to occur, presumably the result of proteolytic cleavage.¹¹⁴ Cells known to express LNGFR include oligodendrocytes,¹¹³ B cells (but not monocytes or T cells),¹¹⁵ bone marrow fibroblasts,¹¹⁶ autonomic and sensory neurons,^{110, 117} Schwann cells,¹¹⁷ follicular dendritic cells,¹¹⁸ select astrocytes,¹¹⁹ and mesenchymal cells involved with mesenchymal-epithelial interactions.¹²⁰

CD40:

CD40 is a 50 kDa, 277 aa residue transmembrane glycoprotein most often associated with B cell proliferation and differentiation.^{121, 122} Expressed on a variety of cell types, human CD40 cDNA encodes a 20 aa residue signal sequence, a 173 aa residue extracellular region, a 22 aa residue transmembrane segment, and a 62 aa residue cytoplasmic domain.¹²² There are four cysteine-rich motifs in the extracellular region that are accompanied by a juxtamembrane sequence rich in serines and threonines. Mouse CD40 is 62% identical to human CD40 at the aa sequence level. However, mouse CD40 is 305 aa residues long with the difference attributable to a 28 aa residue extension in the cytoplasmic tail.¹²³ CD40 ligation is associated with the induction of apoptosis. This is not due the activation of a cytoplasmic "death domain"; rather CD40 ligation can upregulate Fas antigen, which primes cells for subsequent Fas-mediated apoptosis.¹²⁴ Currently, it is believed that the normal signaling pathway of CD40 involves both NF- κ B, and protein kinase (*lyn*) activation.¹²⁵ Soluble CD40 has been identified in B cell cultures, presumably the result of proteolytic processing.^{126, 127} Although many functions have been attributed to CD40, one suggests that CD40 ligation preferentially drives B cells into memory cells rather than plasma cells.¹²⁸ Cells known to express CD40 include B cells,¹²³ monocytes and basophils (but not mast cells),¹²⁹ eosinophils,¹³⁰ endothelial cells,¹³¹ interdigitating dendritic cells,¹³² Langerhans cells,¹³³ blood dendritic cells,¹³⁴ fibroblasts,¹³⁵ keratinocytes,¹³⁶ Reed-Sternberg cells of Hodgkin's disease, and Kaposi's sarcoma cells.^{137, 138} A review on CD40 can be found in reference 121.

CD137/4-1BB/ILA:

Human CD137 is a 30-35 kDa activation-induced glycoprotein that occurs as both a monomer and homodimer on the surface of cells.^{7, 139-141} CD137 is aa residues long, including a 17 aa residue signal sequence, a 169 aa residue extracellular region, a 27 aa residue transmembrane segment, and a 42 aa residue cytoplasmic domain.^{29, 139, 142} In the extracellular region, CD137 contains the characteristic multiple cysteine-rich motif.⁷ Mouse to human, although there is 60% aa sequence identity across the open reading frame,^{29, 143} there is minimal to no cross-species biological activity.^{29, 144} The K_d for CD137L binding to CD137 is reported to be about 30 pM.²⁹ Soluble CD137 is known to exist, but unlike the soluble forms of TNFRI & II, CD40 and LNGFR, it is created by an alternative splicing event.¹⁴⁵ CD137 ligation is reported to interrupt T cell apoptotic programs associated with activation-induced cell death.¹⁴⁶ Cells known to express CD137/4-1BB/ILA (for induced by lymphocyte activation) include fibroblasts,¹⁴⁵ thymocytes,¹⁴⁵ monocytes,^{139, 145} and CD4 $^{+}$ and CD8 $^{+}$ T cells.¹⁴¹

TNFRI/p55/CD120a:

TNFRI is a 55 kDa, 455 aa residue transmembrane glycoprotein that is apparently expressed by virtually

all nucleated mammalian cells.¹⁴⁷⁻¹⁴⁹ The molecule has a 190 aa residue extracellular region, a 25 aa residue transmembrane segment, and a 220 aa residue cytoplasmic domain.^{7, 147} In a comparison of mouse to human proteins, TNFRI has 64% aa sequence identity (70% in the extracellular region), with mouse and human TNFRI binding human and mouse TNF-alpha with equal affinity.^{150, 151} The extracellular region has four cysteine-rich motifs, the first of which is suggested to be required for binding.¹⁵² The cytoplasmic domain has an 80 aa residue "death domain" that can trigger an apoptotic pathway.¹⁵³ This is not the only outcome of TNFRI ligation, however. NF- κ B is also activated by the TNFRI, although the mechanism determining the choice of pathways is not clear.¹⁵⁴ Both TNF-alpha and TNF-beta bind to TNFRI. Soluble TNF-alpha binds with a K_d in the range of 20-60 pM,^{152, 154} while TNF-beta binds with a K_d equal to 650 pM.¹⁵² While TNFRI relative to TNFRII has been suggested to be the more physiologically-relevant receptor, recent evidence suggests that TNFRI is most important for circulating TNF-alpha, while membrane-bound TNF-alpha associates with TNFRII¹⁵⁴ (see TNFRII below). Soluble TNFRI, which blocks TNF-alpha activity, has been identified in both urine and blood (1-3 ng/mL).^{39, 40, 155} Soluble forms of at least two molecular weights (32 kDa and 48 kDa) have been identified and are believed to be generated by proteolytic cleavage.^{149, 156, 157} Among the numerous cells known to express TNFRI are hepatocytes,⁴⁰ monocytes and neutrophils,¹⁵⁸ cardiac muscle cells,¹⁵⁹ endothelial cells,¹⁶⁰ and CD34⁺ hematopoietic progenitors.¹⁶¹

TNFRII/p75/CD120b:

Human TNFRII is a 75 kDa, 461 aa residue transmembrane glycoprotein originally isolated from a human lung fibroblast library.¹⁶² This receptor consists of a 240 aa residue extracellular region, a 27 aa residue transmembrane segment and a 173 aa residue cytoplasmic domain.^{7, 162} Mouse to human, aa sequence identity in TNFRII cytoplasmic domain is 73 %, while aa sequence identity in the extracellular region falls to 58%.¹⁵⁰ This drop in extracellular identity is reflected in the observation that human TNF-alpha is not active in the mouse system.¹⁵⁰ TNFRII to TNFRI, aa sequence identity is only about 20% in the extracellular region and 5% in the cytoplasmic domain.¹⁵⁰ The function of TNFRII is not clear. In the TNF-alpha system, it has been suggested that TNFRII binds TNF-alpha and transfers it to TNFRI, which then is activated and initiates a physiological response.^{163, 164} TNF-alpha binding to TNFRII clearly has an effect on cells, however, inducing apoptosis in rhabdomyosarcoma (skeletal muscle tumor) cells,¹⁶⁵ and cell migration in Langerhans cells.¹⁶⁶ A clue to understanding of TNFRII activity may lie in its binding kinetics. At 37 °C, soluble TNF-alpha binds to TNFRI with a K_d of 20 pM, and to TNFRII with a K_d of 300 pM (note: at 4 °C the K_d 's are approximately equal at 100 and 300 pM respectively). Since TNF-alpha levels (at least systemically) are usually in the range of 100 pM, TNF-alpha activity will normally be mediated by the TNFRI molecule. In addition, a TNF-alpha:TNFRII interaction leads to a very slow oligomerization of receptor molecules, and ligand dissociation seems to occur before receptor-signaling complex formation. Thus, TNFRII could be envisioned to "hand-off" to TNFRI. However, not all TNF-alpha is soluble, and current theory predicts that membrane-bound TNF-alpha is the effective ligand for TNFRII. In this form, a TNF-alpha:TNFRII complex allows time for the slow formation of signal-transducting oligomers.¹⁵⁴ For TNF-beta, the K_d for TNFRII binding is reported to be approximately 300 pM. However, it would appear that a TNF-beta:TNFRII complex is non-signaling, leading to the suggestion that in the TNF-beta system, TNFRII is nothing more than a "decoy-receptor".¹⁶⁷ Soluble forms of TNFRII have been identified, resulting apparently from proteolytic cleavage by a metalloproteinase termed TRRE (TNF-Receptor Releasing Enzyme).^{168, 169} The shedding process appears to be independent of that for soluble TNFRI.¹⁷⁰ Among the multitude of cells known to express TNFRII are monocytes,¹⁷⁰ endothelial cells,¹⁷¹ Langerhans cells,¹⁶⁶ and macrophages.¹⁷²

CD134/OX40/ACT35:

Human OX40 is a 48 kDa, type I (external N-terminus) transmembrane glycoprotein that appears to have a very limited pattern of expression,^{173, 174} currently consisting of only activated CD4⁺ and CD8⁺ T cells.¹⁷⁴ The mature molecule is a 250 aa residue polypeptide that consists of a 188 aa residue extracellular region, a 26 aa residue transmembrane segment, and a 36 aa residue cytoplasmic domain.^{7, 173} In the extracellular region, there is about 60% aa sequence identity human to mouse.^{173, 175} There is marked species cross-reactivity in this system.^{58, 174}

CD27:

Immune system cells are currently the only reported source for expression of CD27, a 50-55 kDa variably glycosylated polypeptide.^{176, 177} The mature molecule has a predicted molecular weight of 27 kDa and is 242 aa residues long, consisting of a 175 aa residue extracellular region, a 21 aa residue transmembrane segment, and a 46 aa residue cytoplasmic domain.^{7, 176} Mouse to human, CD27 is 65% identical at the aa

sequence level, with both molecules expressed as homodimers on the cell surface.^{176, 178} Although CD27 lacks a recognizable cytoplasmic "death-domain" motif, it can induce apoptosis through a receptor-associated, death-domain containing a cytoplasmic protein known as Siva (the Hindu god of destruction).¹⁷⁹ Whether there are a number of such proteins specific for various TNFRSF members remains to be seen. A soluble, 32 kDa form of CD27 has been identified in both blood and urine, most likely the result of proteolytic processing.^{177, 180} Cells known to express CD27 include NK cells,¹⁸¹ B cells,^{182, 183} CD4⁺, CD8⁺ T cells and thymocytes.¹⁷⁶

Fas/CD95/APO-1:

Human Fas (fibroblast associated) is a 43 kDa, 355 aa residue transmembrane glycoprotein found on multiple cell types.¹⁸⁴ Also known as APO-1 (for Apoptosis-1), the molecule appears to be more than a simple mediator of apoptosis. On fibroblasts, Fas ligation can lead to either proliferation or apoptosis depending on the relative number of expressed Fas molecules.¹⁸⁵ The human receptor is 335 aa residues long, with a 156 aa residue extracellular region, a 20 aa residue transmembrane segment, and a 144 aa residue cytoplasmic domain.^{7, 184} In the extracellular region, there are three cysteine-rich motifs, while in the cytoplasmic region there is a 68 aa residue "death-domain", which is also found in (and 25% identical to) the TNFRI cytoplasmic region.^{153, 186} It is currently suggested that cytoplasmic death-domain containing proteins associate with this area (FADD protein with Fas, TRADD protein with TNFRI), thereby transmitting apoptotic signals.¹⁸⁷ Both FADD and TRADD are also known to associate with each other, suggesting considerable interaction between the apoptotic programs of each system.¹⁸⁷ There is 50% aa sequence identity in Fas molecules, mouse to human, with mouse Fas being eight aa residues shorter in length.¹⁸⁸ Soluble forms of Fas are known, the result of alternative gene splicing.^{189, 190} In blood, soluble Fas is reported to circulate as a dimer and trimer at low ng/mL concentrations.¹⁹⁰ Cells reported to express Fas include CD34⁺ stem cells,¹⁶¹ fibroblasts,¹⁸⁵ NK cells,¹⁹¹ keratinocytes,⁹² hepatocytes,¹⁹³ B cells and B cell precursors,¹⁹⁴ monocytes plus CD4⁺ and CD8⁺ T cells,¹⁹⁵ CD45RO⁺ ?d T cells,¹⁹⁶ eosinophils,¹⁹⁷ and thymocytes, with low levels detected on CD4⁻CD8⁻ precursors, and high levels on CD4⁺CD8⁺ precursors.¹⁹⁸ A review on Fas can be found in reference #199.

CD30/Ki-1:

Human CD30 is a 105-120 kDa transmembrane glycoprotein often associated with the Reed-Sternberg cells of Hodgkin's disease.^{200, 201} Although in most cases, mouse to human, members of the TNFRSF are close in terms of overall length, CD30 shows a marked departure from the norm. Mature human CD30 is 577 aa residues long, with an 18 aa residue signal sequence, a 365 aa residue extracellular region, a 24 aa residue transmembrane segment, and a 188 aa residue cytoplasmic domain.²⁰⁰ There are six cysteine-rich motifs in the extracellular region. In mice, mature CD30 is 480 aa residues long, with a 90 aa residue deletion in the extracellular region relative to the human.²⁰² This 90 aa residue differential eliminates three of the six cysteine-rich motifs found in humans.²⁰² Overall, there is approximately 60% aa sequence identity, mouse to human.²⁰² An 85 kDa form of soluble CD30 has been detected in the blood of patients with CD30⁺ lymphomas.²⁰³ Cells known to express CD30 include Reed-Sternberg cells,²⁰¹ CD8⁺ T cells,²⁰² and CD4⁺ T cells.²⁰⁴ Of note, CD30⁺ CD4⁺ T cells are considered to be major producers of T cell-derived IL-5.²⁰⁴

LT-beta R:

Human LT-beta R (lymphotoxin-beta receptor) is a 75 kDa transmembrane glycoprotein that consists of a 201 aa residue extracellular region, a 26 aa residue transmembrane segment, and a 187 aa residue cytoplasmic domain.^{7, 205, 206} In the extracellular region, it contains four cysteine-rich motifs. A comparison of mouse to human receptors shows 76% identity at the aa sequence level.²⁰⁶ In terms of ligands, LT-beta R preferentially binds (TNF-beta)₁(LT-beta)₂ heterotrimers over LT-beta homotrimers. Mouse ligands are active on human receptors while human ligands are only marginally active on mouse receptors.²⁰⁶ Relative to the TNFR receptors, LT-beta R is most like TNFRI in the first two cysteine-rich motifs, and most like TNFRII in the third and fourth cysteine-rich motifs.²⁰⁶ LT-beta R is known both to activate NF-?B and to induce cell death via TRAF-3, making it somewhat analogous to TNFRI.²⁰⁷ Genes known to be activated by LT-beta R include IL-8 and RANTES.²⁰⁸ Based on cell lines, LT-beta R is found on monocytes, fibroblasts, smooth muscle and skeletal muscle cells.²⁰⁸

DR3/WSL-1/TRAMP/APO-3/LARD:

DR3 (or Death Receptor 3) is a 54 kDa, 417 aa residue type I (external N-terminus) transmembrane glycoprotein that has been isolated under a variety of names.²⁰⁹ The DR3 designation results from this

being the third factor discovered with an intracellular "death domain", TNFRI being the first and Fas being the second.²⁰⁹ Also known as APO-3,²¹⁰ Wsl-1,²¹¹ LARD (lymphocyte-associated receptor of death),²¹² and TRAMP (TNFR-related apoptosis mediating protein),²¹³ this molecule appears to be somewhat analogous to TNFRI in that it can activate both NF-?B and induce apoptosis.^{209, 213} The receptor has a 24 aa residue signal sequence, a 178 aa residue extracellular region, a 23 aa residue transmembrane segment, and a 192 aa residue cytoplasmic domain.^{209, 210} In the extracellular region there are four cysteine-rich motifs.²¹⁰ At the aa sequence level, DR3 is approximately 30% identical to TNFRI, and 25% identical to Fas.²¹⁰ About a dozen alternate splice forms are known for DR3, many coding for potentially soluble forms.²¹¹⁻²¹³ The shorter isoforms seem to be expressed by resting cells that subsequently switch to expressing the full-length (413 aa residues) isoform upon activation.²¹² Cells identified as expressing DR3 include T and B cells²¹² and HUVECs (human umbilical vein endothelial cells). A HUVEC library was used to clone DR3.²⁰⁹ There is currently no known ligand for DR3.

DR4:

DR4 (or Death Receptor 4) is one of three known receptors for TRAIL.²¹⁴ DR4 is a 468 aa residue type I (extracellular N-terminus) transmembrane protein that contains a 23 aa residue signal sequence, a 226 aa residue extracellular region, a 19 aa residue transmembrane segment, and a 220 aa residue cytoplasmic domain. In the extracellular region, there are two cysteine-rich motifs.²¹⁴ Although DR4 has a death-domain, it cannot activate NF-?B, and it cannot use FADD, a death domain-associated cytoplasmic protein utilized by Fas, TNFRI and DR3.²¹⁴ To date, it is only known to be expressed by activated T cells.²¹⁴

DR5:

DR5 (or Death Receptor 5) is the second of three known receptors for TRAIL.²¹⁵ Like DR4, ligation of this receptor can trigger an apoptotic program independent of FADD participation. The molecule is 411 aa residues long, with a very large 51 aa residue signal sequence, a 132 aa residue extracellular region, a 22 aa residue transmembrane segment, and a 206 aa residue cytoplasmic domain. The extracellular region contains two cysteine-rich motifs.²¹⁵

DcR1/TRID:

DcR1 (Decoy Receptor-1)²¹⁶ or TRID (TRAIL Receptor without an Intracellular Domain)²¹⁵ is exactly what the latter name suggests, *i.e.*, a membrane-bound receptor for TRAIL that possesses no cytoplasmic domain. Found on endothelial cells and lymphocytes, the molecule is 259 aa residues long, possessing a 23 aa residue signal sequence, a 217 aa residue extracellular region, and a 19 aa residue transmembrane domain.²¹⁵ There are two cysteine-rich motifs in the extracellular region, which is 50-60% identical at the aa sequence level to the same regions in DR4 and DR5. Without a cytoplasmic segment, this receptor does not signal. Instead, it inhibits responsiveness to TRAIL at the level of the cell membrane.

TR2:

TR2 is a newly discovered, 32 kDa type I transmembrane glycoprotein that has no known ligand at present.²¹⁷ Found on T cells, B cells, monocytes and endothelium, the molecule is 283 aa residues long, with a 36 aa residue signal sequence, a 165 aa residue extracellular region, a 23 aa residue transmembrane segment, and a 59 aa residue cytoplasmic domain. The extracellular region contains four cysteine-rich motifs.²¹⁷

GITR:

GITR (glucocorticoid-induced TNFR family-related) is a 228 aa residue transmembrane protein that is suggested to be a close relative of 4-1BB and CD27. Inducible during T cell activation, the molecule has a 19 aa residue signal sequence, a 134 aa residue extracellular region, a 23 aa residue transmembrane segment and a 52 aa residue cytoplasmic domain. It has three cysteine-rich motifs in its extracellular region. Like 4-1BB, ligation interrupts TCR-DC3-induced apoptosis in T cells.²¹⁸

Osteoprotegerin/OPG:

Named because of its ability to protect bone from breakdown (*i.e.*, inhibit osteoclasts), OPG is a 55 kDa, 380 aa residue, naturally secreted member of the TNFRSF.²¹⁹ Most similar to TNFRII and CD40, this

"receptor" has no transmembrane segment, and circulates as a disulfide-linked homodimer. The human, mouse and rat proteins are all equal in length, with human and rat having 94% aa sequence identity. It is unknown what type of "ligand" exists for this receptor.

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